

## Ectopic Pregnancy: Risk Factors, Clinical Presentation and Management

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### About the Author



**Dr. G. Geovin Ranji** did her MS DGO from Government Medical College, Kozhikode. She was assistant professor during the study. She is interested in infertility and high-risk pregnancy.

### Abstract

**Background** Ectopic pregnancy is increasing in incidence. Nevertheless, there is wide availability of tools for early diagnosis and advances in management. Though it is not a

leading cause of maternal mortality, it significantly causes morbidity and jeopardizes reproductive outcome in women desirous of fertility.

**Aims** To determine incidence, risk factors, symptoms, signs, type of ectopic pregnancy and management.

**Settings and Design** This is a one-year prospective, descriptive study conducted in Department of Obstetrics and Gynaecology, Sri Ramachandra Medical College and Research Institute, Porur, Chennai.

**Results** There were 119 ectopic pregnancies during the study period. The incidence of ectopic pregnancy is 2.81/100 deliveries. Ectopic pregnancy was common in 26–30 years, the minimum age at diagnosis was 18 years and maximum age was 40 years. Fourteen women had previous one ectopic pregnancy. Four had previous two ectopic pregnancies. Previous cesarean and treatment for infertility were the commonest risk factors. The classic

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triad was present in only 27.7% of patients. Fourteen patients presented with shock. Five women were diagnosed even before they missed their periods. Success rate of medical treatment with methotrexate is 83.33%. Tubal pregnancy was the commonest type, and ampulla was the commonest site. Right side was affected more than left side. Thirty-three patients (27.7%) required blood transfusion. Seven developed morbidity. After 1-year follow-up of 68 women who were desirous of fertility, five women have become pregnant subsequently with intrauterine gestation.

**Keywords** Ectopic pregnancy · hCG · Methotrexate · Tubectomy · Laparoscopy

## Introduction

An ectopic or extrauterine pregnancy is defined as implantation of blastocyst anywhere other than the endometrial lining of the uterine cavity [1]. The earlier works by Busiere (1693) and Gifford (1731) recognized it as one of the most serious complications of pregnancy [2]. The signs and symptoms of an ectopic pregnancy when unruptured mimic that of a normal pregnancy. However, the classic triad of symptoms of an ectopic pregnancy includes abdominal pain, bleeding per vaginum and amenorrhea/positive urinary pregnancy test. The signs and symptoms of an ectopic pregnancy vary based on whether it is ruptured or not. The standard diagnostic criteria for ovarian, interstitial, primary abdominal and cervical pregnancy are given by Spiegelberg [3], Timor-Tritsch [2], Studdiford [2] and Rubin [2], respectively.

Management depends on hemodynamic status, future fertility, the levels of  $\beta$ -hCG, status of the tube (ruptured/unruptured) and ultrasonographic findings.

## Materials and Methods

The study will aid in early diagnosis of ectopic pregnancy and minimize morbidity associated with early diagnosis. By studying the risk factors, this will help in focusing on the high-risk group to prevent mortality and guide in standardizing management protocol for further cases.

This was a prospective, descriptive study carried out from April 2014 to March 2015 at Department of Obstetrics and Gynaecology, Sri Ramachandra Medical College and Research Institute, Porur, Chennai. Women who presented in our outpatient department and emergency department with clinical features of ectopic pregnancy and in whom diagnosis was confirmed during the clinical course were included in the study. Women who had intrauterine pregnancy, who were not willing to participate

in the study and who got discharged against medical advice and got treated elsewhere were excluded from the study.

During the study period of April 2014 to March 2015, women who presented in our outpatient department and emergency department with clinical features of ectopic pregnancy were enrolled in our study. Their clinical profile including name, age, marital status, parity and last child birth was noted. History of relevant risk factors was taken. Detailed history of symptoms was noted. All patients were examined systematically, and vitals were recorded. Signs suggestive of ectopic pregnancy were looked for. All women who had clinical suspicion of ectopic pregnancy underwent the triad of investigations—urine pregnancy test, serum  $\beta$ -hCG and transvaginal ultrasound. Depending upon the clinical presentation and  $\beta$ -hCG, patients were streamlined to be managed conservative/expectant, medical and surgical laparoscopy/laparotomy management. Patient and attenders were explained the same, and an informed written consent was obtained.

Women who presented in shock were urgently resuscitated, investigations sped up, and after confirming diagnosis, they underwent emergency laparotomy. During laparotomy, standard protocol was followed. Selected patients with unruptured ectopic pregnancy who were clinically stable and whose  $\beta$ -hCG was beyond 5000 IU/L were successfully managed with laparoscopic salpingectomy/salpingotomy.

Patients who were clinically stable and whose initial  $\beta$ -hCG was  $< 1000$  IU/L were conservatively managed and followed up with serial  $\beta$ -hCG repeated after 48 h. If it shows a declining trend, a diagnosis of failing pregnancy was made and followed up with serial weekly  $\beta$ -hCG until normal or adequate fall. If it increases more than the discriminatory zone, transvaginal ultrasound was repeated and further planned accordingly.

Patients whose  $\beta$ -hCG were  $< 2000$  IU/L were given single-dose methotrexate and whose  $\beta$ -hCG were  $> 2000$  IU/L were given multiple-dose regime methotrexate. When medical treatment fails despite four doses of methotrexate, increasing trend of  $\beta$ -hCG on day 7, detection of cardiac activity and patient developing clinical evidence of ruptured ectopic pregnancy; surgical treatment was sorted to.

Patients who underwent surgical management were treated with blood transfusion, antibiotics and supportive care. Those who needed ventilator support for stabilization were managed in ICU. Measures to prevent complications in the postoperative period were taken.

Women who were desirous of fertility were followed up for 1 year after treatment and their reproductive outcome was analyzed. Data were entered in MS Excel and analyzed by SPSS 20.0.

## Results

There were 119 ectopic pregnancies during the study period. The incidence of ectopic pregnancy is 2.81/100 deliveries. Ectopic pregnancy was common in 26–30 years (54.6%), the minimum age at diagnosis was 18 years and maximum age was 40 years with a mean age of 28.79 years and SD of 4.256.

Most of the patients were primigravida—47 in number. Maximum last childbirth noted was 19 years. 47.1% of ectopic pregnancies occurred within 2–5 years of last child birth. Five women were diagnosed even before they missed their periods. They were detected earliest because three women had undergone treatment for infertility and two reported earlier as they had a previous ectopic pregnancy. Maximum gestation age at detection was 133 days in an unbooked patient whose cervical pregnancy was missed at her first trimester elsewhere. She eventually underwent hysterectomy due to uncontrolled hemorrhage. Most of the ectopic pregnancies (30%) were diagnosed at gestation age of 8–10 weeks (Tables 1, 2, 3, 4, 5 and 6).

Eighteen (19.6%) patients had previous ectopic pregnancies. Fourteen women had previous one ectopic pregnancy. Four had previous two ectopic pregnancies. Five of them had previous salpingectomy. Thirty-three had medical management of previous ectopic pregnancy. Previous

**Table 1** Clinical and demographic data

	Number	Percent
Age group		
< 20	2	1.68
21–25	20	16.8
26–30	65	54.6
31–35	23	19.33
> 35	9	7.56
Gravida		
Primi	47	39.5
Multi	72	60.5
Last child birth		
≤ 1 year	5	9.8
2–5	24	47.1
6–10	15	29.4
> 11	7	13.7
Gestation age		
< 4 weeks/no missed period	5	4.2
4–5	12	10.1
5–6	16	13.4
6–7	20	16.8
7–8	28	23.5
> 8	36	30.2
Gestation age not known	2	1.7

**Table 2** Risk factors

	Number	Percent
Previous CS	29	31.5
Previous ectopic	18	19.6
Sterilized	11	11.95
Recanalized	2	2.1
Treatment for infertility	29	31.5
IUCD	3	3.3

**Table 3** Symptoms and signs

	Number	Percent
Amenorrhea	114	95.8
Vaginal bleeding/spotting	49	41.2
Abdominal pain	74	62.2
Fainting attack	14	11.8
Triad	33	27.7
All four	8	6.72
Signs		
Abdominal tenderness	81	68.1
Pelvic tenderness	53	44.5
Shock	14	11.8
Adnexal mass	6	5
All signs	9	7.6

cesarean and treatment for infertility were the commonest risk factors. The other risk factors noted were previous ectopic pregnancy, sterilization, recanalization and IUCD usage.

The classic triad was present in only 27.7% of patients. Fourteen (11.8%) patients presented with shock. Abdominal tenderness was the commonest sign in 81 (68.1%) patients.

Tubal pregnancy (81.5%) was the commonest type, and ampulla was the commonest site. Right side was affected more than left side. In 14 patients, site was not diagnosed; one was PUL (pregnancy of unknown location), two were failing ectopic and eleven had heteroechoic mass in the POD; side could not be ascertained and underwent medical management.

The commonest procedure done was emergency laparotomy and salpingectomy in 50 (78.1%) patients. Ten (15.6%) women were successfully managed laparoscopically. Success rate of medical treatment with methotrexate is 83.33%. Patients who got multiple-dose regimen of methotrexate and who developed morbidity after surgical management had the longest stay, while patients managed by laparoscopy stayed in the hospital for the shortest period.

Thirty-three patients (27.7%) required blood transfusion. One patient required 3 FFP transfusions for the correction of DIC.

**Table 4** Type of ectopic pregnancy

Diagnosis	Number	Percent
Unruptured	54	45.4
Ruptured	55	46.2
Tubal abortion	6	5
Failing ectopic	2	1.6
PUL	1	0.8
Chronic	1	0.8
Site		
Tubal	97	81.5
Ovarian	–	
Heterotopic	2	1.7
Cornual	4	3.4
Cervical	1	0.8
Scar ectopic	1	0.8
Tubal		
Ampullary	31	31.9
Isthmial	4	4.1
Fimbria	3	3.1
Isthmo-ampullary	8	8.3
Site not known (unruptured)	51	52.6
Side		
Right	67	61
Left	43	39

**Table 5** Management

	Number	Percent
Expectant	19	15.9
Medical	35	29.4
Surgical	57	47.9
Expectant + medical	1	0.8
Medical + surgical	7	5.9
Surgical		
Laparoscopy	10	15.6
Cornuotomy	1	1.5
Hysterectomy	1	1.5
Salpingectomy	50	78.1
Salpingostomy	1	1.5
Segmental resection	1	1.5

Four patients required ICU admission following laparotomy for need of intensive monitoring. One woman developed TRALI (transfusion-related acute lung injury) following transfusion of seven pints. One patient suffered from DIC, and one woman needed hysterectomy for control of hemorrhage from undiagnosed cervical pregnancy. There were no deaths due to ectopic pregnancy in the study period.

## Discussion

During the study period, there were 119 cases of ectopic pregnancy and there were 4233 deliveries. This gives the incidence of 2.81/100 deliveries. Of the 119 women included in the study, two were unmarried. This must be emphasized for suspecting ectopic pregnancy irrespective of marital status. Diagnosis can be made certain with the use of urine pregnancy test, serum  $\beta$ -hCG and ultrasound after a dedicated history taking and clinical examination. Forty-seven (39.5%) patients were primigravida. Sixty-eight women had no living children. The selection of appropriate management in these women is important in optimizing their further reproductive outcome. Maximum last childbirth noted was 19 years in a sterilized patient. 47.1% of ectopic pregnancies occurred within 2–5 years of last child birth. 9.8% of ectopic pregnancies occurred within 1 year of delivery.

The common risk factors noted were previous cesarean (31.5%) and treatment for infertility (31.5%). Eighteen (15%) patients did not have any risk factors. No patients had past/family history of tuberculosis. One patient had taken MTP pill without a prior scan for location of gestation sac. Eighteen (19.6%) patients had previous ectopic pregnancies. Five of them had undergone previous salpingectomy on the opposite side. Thirteen had medical management of previous ectopic pregnancy. In a Polish study [4] by Kostrzewa et al. who compared women's fertility after surgical treatment of tubal ectopic pregnancy during a 24-month follow-up, recurrent risk of ectopic in 13.6% cases following salpingotomy versus 19.4% following salpingectomy. In another study by de Bennetot et al. [5], the 2-year cumulative rate of recurrences was 18.5% after salpingostomy or salpingectomy and 25.5% after medical treatment. Of the 11 sterilized, three were concurrent sterilization with LSCS, seven were puerperal sterilization and one was laparoscopic sterilization. Of the 29 who had undergone treatment for infertility, three had undergone IVF-ET, five had undergone IUI and 21 had undergone ovulation induction only. This group of patients should be diagnosed without delay, treatment must be customized and further fertility treatment is to be planned with caution. This is also stressed by the review article by Refaat et al. [6]. Of the three women who had IUCD, all the three were copper containing. When a woman misses her periods with an IUCD in situ, ectopic pregnancy should be carefully sought for. In a multicenter, case–control study conducted in China [7], it is concluded that in addition to the traditional risk factors, IVF-ET and current IUCD use play dominant roles in the occurrence of ectopic pregnancy.

**Table 6** Blood transfusion

Number of pints	Number
1	11
2	12
3	4
4	4
5	1
7	1
Total	33

Maximum ectopic pregnancies occurred in November (15), and the least occurred in July (6). All women underwent the three investigations—urine pregnancy test, serum  $\beta$ -hCG and transvaginal ultrasound. The mean  $\beta$ -hCG in ruptured ectopic was 18,629, which is higher than the mean  $\beta$ -hCG in unruptured ectopic which was 6889. This was statistically significant ( $p$  value 0.008). This result is similar to the Iranian study on predictive value of maternal serum  $\beta$ -hCG concentration in the ruptured tubal ectopic pregnancy ( $p = 0.03$ ) [8] proving that higher  $\beta$ -hCG is associated with ruptured ectopic pregnancy. In all patients except one, transvaginal ultrasound was diagnostic. That exceptional one patient was a case of cervical pregnancy who presented to us late as an unbooked case with hemorrhage.

Fifty-four cases were unruptured ectopic and 55 cases were ruptured ectopic pregnancies. Six were tubal abortion. One case turned out to be pregnancy of unknown location (PUL), and there was one case of chronic ectopic. The commonest site was tubal—97 patients (81.5%). There were two cases of heterotopic pregnancies, four were cornual pregnancies, one case was cervical pregnancy and one was scar ectopic. There was no case of ovarian or abdominal pregnancy during the study. Of the 97 tubal ectopic pregnancies, 31 were ampullary, eight were at the isthmo-ampullary junction, four were isthmal and three were fimbrial.

Twenty patients were allotted for expectant/conservative management. Of them, only one patient needed single-dose methotrexate in view of doubling  $\beta$ -hCG. The success rate of conservative management in our study is 95%. In properly selected cases, expectant management has similar success rates comparable to medical management with methotrexate [9]. Of the 42 patients who were allotted to medical management, 7 needed surgical treatment. Success rate of methotrexate is 83.33%. A majority of 64 patients (53.8%) were managed surgically including the seven who needed surgery following failed medical treatment. The commonest procedure done was emergency laparotomy and salpingectomy in 50 (78.1%) patients. Ten (15.6%) women were successfully managed laparoscopically. One

case of cervical pregnancy needed emergency hysterectomy, and one case of cornual pregnancy was successfully managed by the novel cornuotomy [10].

One patient who had isthmal pregnancy was treated with segmental resection. Salpingostomy was done in only one patient. Whether salpingostomy or salpingectomy is the appropriate procedure has not been studied in RCTs and is still under debate [11]. Also RCOG guidelines state in the presence of a healthy contralateral tube; there is no clear evidence that salpingotomy should be used in preference to salpingectomy [12]. Hence surgical management should be individualized depending upon the hemodynamic status, concern for future fertility and the presence of a healthy contralateral tube.

After 1-year follow-up of 68 women who were desirous of fertility, five women have become pregnant. All were subsequent intrauterine pregnancies. Of the five women, one was following conservative management, three were following medical management and one was following salpingectomy. In a population-based study by de Bennetot et al. [5] to analyze fertility following ectopic pregnancy, the 24-month cumulative rate of intrauterine pregnancy was 67% after salpingectomy, 76% after salpingostomy and 76% after medical treatment. The study recommends conservative treatment over radical strategy. In another study by Juneau and Bates [13], the authors conclude that the most predictive factor of future fertility is the health of the contralateral tube.

## Conclusions

As ectopic pregnancy is common in reproductive age group, it should not be missed in extremes of age. It should be suspected in women with risk factors. In our study, we could identify five women even before they missed their periods due to the knowledge of their risk factors. The classic triad of amenorrhea, vaginal bleeding/spotting and abdominal pain were present in only 27.7% of patients. Diagnosis can be made certain with the use of urine pregnancy test, serum  $\beta$ -hCG and ultrasound after a dedicated history taking and clinical examination. Surgical management should be individualized depending upon the hemodynamic status, concern for future fertility and the presence of a healthy contralateral tube. The selection of appropriate management in those women without living children is important in optimizing their further reproductive outcome.

## Compliance with Ethical Standards

**Conflict of interest** Geovin Ranji, UshaRani and SriVarshini declare that they have no conflict of interest.

**Ethical Approval** All procedures followed were in accordance with the ethical standards of the institutional committee and with the Helsinki Declaration of 1975, as revised in 2008.

**Informed Consent** Informed consent was obtained from all patients for being included in the study.

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